

Clinical effects of potential drug-drug interactions in hemorrhagic stroke patients admitted to the emergency department

Drug interactions in hemorrhagic stroke

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Abstract

Aim: Hemorrhagic stroke is a medical condition characterized by non-traumatic intracranial bleeding, leading to high mortality and morbidity, and is frequently diagnosed in emergency departments. Its prevalence varies between countries, highlighting the importance of investigating modifiable risk factors. Drug-drug interactions (DDIs) may contribute to its development. This study aims to evaluate the medications used by hemorrhagic stroke patients over the past six months, assess potential DDIs, and examine their relationship with age, sex, and clinical parameters.

Materials and Methods: A retrospective analysis was conducted on patients diagnosed with hemorrhagic stroke both radiologically and clinically in the emergency department. Patients were categorized into three groups: hemorrhagic stroke risk interaction, non-risk interaction, and no interaction.

Results: Of 198 patients, 68% were male and 32% female, with a mean age of 61.93 ± 18.2 years. Chronic disease was present in 67.6% of patients; hypertension was the most common. At least one medication was used by 56.1%, and 49.5% of them had DDIs. Overall, DDIs were identified in 27.7% of all patients. Patients with hemorrhagic stroke risk interactions were significantly older ($p < 0.001$) and had more comorbidities ($p < 0.0001$). Hypertension was significantly more frequent in this group ($p < 0.0001$). Risk-related DDIs included 30 associated with elevated blood pressure, 12 with bleeding, and 2 with arrhythmia.

Discussion: DDIs are a modifiable risk factor in hemorrhagic stroke. Medication histories should be carefully reviewed, particularly in elderly, multimorbid patients. Caution is essential in patients using antihypertensives, and polypharmacy should be minimized to reduce interaction risks.

Keywords

hemorrhagic stroke, emergency department, drug-drug interaction

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Introduction

Emergency departments are the primary units where patients with life-threatening conditions are first admitted, representing some of the busiest and most critical services within hospitals. One of the major diagnoses made in emergency departments is stroke, and a significant proportion of patients receive their stroke diagnosis in this setting [1]. Stroke is a medical condition characterized by cell death due to insufficient blood flow to a part of the brain [2].

Stroke is divided into two groups: ischemic and hemorrhagic stroke, which is responsible for 13% of all stroke cases, is a neurological condition caused by bleeding into the brain tissue [3,4]. Patients who experience a hemorrhagic stroke are reported to have more severe neurological impairments and higher mortality rates compared to those with ischemic stroke [5]. Stroke prevalence is higher in low- and middle-income countries, and mortality due to hemorrhagic stroke ranges between 25–30% in high-income countries, whereas it varies between 30–48% in low- and middle-income countries [6]. This disparity suggests that modifiable risk factors such as inadequate blood pressure control, delayed access to healthcare, and lack of appropriate treatment are not sufficiently managed in lower-income settings. Indeed, controlling high blood pressure—one of the most important modifiable risk factors—has been shown to significantly reduce the risk of recurrent stroke [7,8].

The literature highlights drug-drug interactions (DDIs) as one of the contributing factors to the failure of antihypertensive treatment [9,10]. A drug-drug interaction is defined as the effect that occurs when two or more drugs are administered concurrently and influence each other's pharmacological or pharmacokinetic properties [11]. Among the potential DDI-related contributors to hemorrhagic stroke are increased bleeding risk, impaired platelet function, concurrent use of antithrombotic agents, neglect of age-related pharmacokinetic changes, and drug combinations that may induce cardiac arrhythmias [12–17].

However, current literature lacks sufficient data evaluating the frequency and clinical consequences of DDIs in patients who have experienced a hemorrhagic stroke. In particular, the extent to which the concomitant use of anticoagulants, antiplatelet agents, and NSAIDs increases the risk of intracranial hemorrhage that may lead to hemorrhagic stroke has not been clearly established. Furthermore, inadequate blood pressure control due to polypharmacy or the emergence of rhythm disturbances are also considered possible mechanisms contributing to the development of hemorrhagic stroke. These potential relationships have been addressed only to a limited extent in the context of DDIs in the existing literature.

This study aims to analyze the medications used in the last six months by patients diagnosed with hemorrhagic stroke in the emergency department, to evaluate the frequency of potential DDIs, the associations between interaction severity and patients' age, sex, and certain clinical parameters (e.g., prognosis, length of hospital stay), and to assess the possible contribution of these interactions to the development of hemorrhagic stroke. The data obtained may support the development of safer drug management strategies in patients at risk for hemorrhagic stroke and provide guidance to clinicians regarding high-risk

drug combinations.

Materials and Methods

Study Design and Population

This study was conducted as a retrospective analysis. Following the approval of the Ethics Committee for Non-Interventional Research at Kırklareli University Faculty of Medicine (approval number: P20250032R01), the study was initiated at Kırklareli Training and Research Hospital.

The study population consisted of patients who were diagnosed with hemorrhagic stroke both radiologically and clinically in the Emergency Department of Kırklareli Training and Research Hospital between January 1, 2023, and December 31, 2024, and who met the inclusion criteria.

Inclusion Criteria

- Patients diagnosed with hemorrhagic stroke in the emergency department between 01/01/2023 and 31/12/2024
- Individuals aged 18 years or older
- Patients for whom a brain computed tomography (CT) was requested
- Patients with a confirmed diagnosis of hemorrhagic stroke based on clinical and radiological findings
- Patients with complete medication information available in the hospital information management system

Exclusion Criteria

- Patients diagnosed with ischemic stroke
- Patients under 18 years of age
- Patients for whom brain CT was not performed
- Patients with incomplete or inaccessible medical records

Data Collection and Drug-Drug Interaction Assessment

During the data collection process, demographic information (age, sex), date of hospital admission, diagnosis, current medication list at the time of admission, and comorbidities were retrieved from the electronic patient record system. Information on medications used regularly within the last 6 months was obtained from prescription records and discharge summaries.

The collected medication data were classified into major, moderate, and minor interaction categories using Drugs.com, a widely used and clinically validated drug interaction classification system. In addition, patients were categorized into three groups based on the potential hemorrhagic stroke risk associated with their drug interactions: (1) interactions with an increased risk of hemorrhagic stroke, (2) interactions not associated with hemorrhagic stroke risk, and (3) no detected drug interactions.

Statistical Analysis

Statistical analyses were performed using GraphPad Prism version 8.0. Descriptive statistics were expressed as mean $\pm$ standard deviation or median (minimum–maximum) for continuous variables, and as number and percentage (%) for categorical variables. To assess the relationship between the presence of potential drug-drug interactions and patient characteristics (age, sex, comorbidities, prognosis, length of hospital stay, hemorrhage localization), the Chi-square test or Fisher's Exact test (where appropriate) was used for categorical variables. For comparisons between continuous and categorical variables, the Independent Samples t-test or Mann-Whitney

U test was applied. For comparisons among more than two groups, ANOVA or the Kruskal-Wallis test was utilized. A p-value of <0.05 was considered statistically significant.

Ethical Approval

This study was approved by the Ethics Committee of Non-Interventional Research at Kırklareli University, Faculty of Medicine (Date: 2025-07-17, No: P20250032R01).

Results

When examining the demographic data of the 198 patients included in the study, it was found that 68% (135) of the patients with hemorrhagic stroke were male, while 32% (63) were female. The mean age of male patients was 59.38 ± 17.9 years, and the mean age of female patients was 67.5 ± 17.9 years. The overall mean age of all 198 patients was 61.93 ± 18.2 years. When the presence of chronic diseases was evaluated, 134 patients (67.6%) were found to have at least one chronic condition, while 64 patients (32.4%) had no chronic disease. The most frequently observed chronic diseases were hypertension (87 patients), diabetes mellitus (33 patients), and coronary artery disease (23 patients), respectively. Based on bleeding localization, the classification of patients was as follows: 47 patients had subarachnoid hemorrhage (SAH), 45 had subdural hematoma, 10 had epidural hematoma, 63 had intracerebral hemorrhage, and 4 had intraventricular hemorrhage. Hemorrhage in other locations was detected in 29 patients. Regarding the length of hospital stay, the mean duration was found to be 15.6 days. In terms of prognosis, 136 patients (68.7%) were discharged, while 62 patients (31.3%) died (Table 1). When the medication use of the patients within the last six months was examined, it was found that 87 patients

(43.9%) had not used any medication, while 111 patients (56.1%) had used at least one medication. In the drug-drug interaction analysis, drug-drug interactions were identified in 55 (49.5%) of the 111 patients who had used medication, and the overall rate of patients with detected drug-drug interactions among all patients was 27.7% (Figure 1). A total of 111 drug-drug interactions were identified in 55 patients in whom drug interactions were detected. When classified according to severity, 24 were minor, 82 were moderate, and 5 were major interactions (Table 2). When patients were categorized according to the presence of drug interactions, 143 patients had no drug-drug interactions, 23 patients had interactions that did not pose a risk for hemorrhagic stroke, and 32 patients had interactions associated with an increased risk of hemorrhagic stroke (Table 3). A significant difference was observed in age distribution among the three groups classified based on drug interaction status (Kruskal-Wallis test, p < 0.001). According to the results of Dunn's multiple comparisons test, the mean age of patients without any drug interactions was found to be significantly lower than that of the group with interactions associated with a risk of hemorrhagic

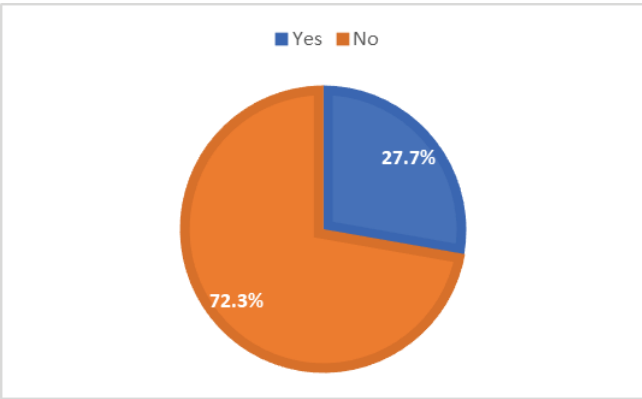


Figure 1. Distribution of drug interactions in the total patient population

Table 1. Patient profile and classification by hemorrhage localization

Variables	Mean (SD) / n (%)
Age (years)	61.93 ± 18.2
Sex	Male: 135 (%68.2), Female: 63 (%31.8)
Mean Age (by Sex)	Male: 59.38 ± 17.9 Female: 67.5 ± 17.9
Presence of Chronic Diseases	Yes: 134 (%67.6), No: 64 (%32.4)
	Intracerebral: 63 (%31.8)
	Subarachnoid: 47 (%23.7)
Site of Hemorrhage	Subdural: 45 (%22.7)
	Epidural: 10 (%5.1)
	Intraventricular: 4 (%2.0)
	Other*: 29 (%14.6)
Length of Hospital Stay (days)	15.6
Prognosis	Discharged: 136 (%68.7), Exitus: 62 (%31.3)
*Intraparenchymal hemorrhage, brainstem hemorrhage, cerebellar hemorrhage	

Table 2. Distribution of drug-drug interactions by severity

Interaction Severity	Number of Interactions (n)
Minor	24 interactions
Moderate	82 interactions
Major	5 interactions

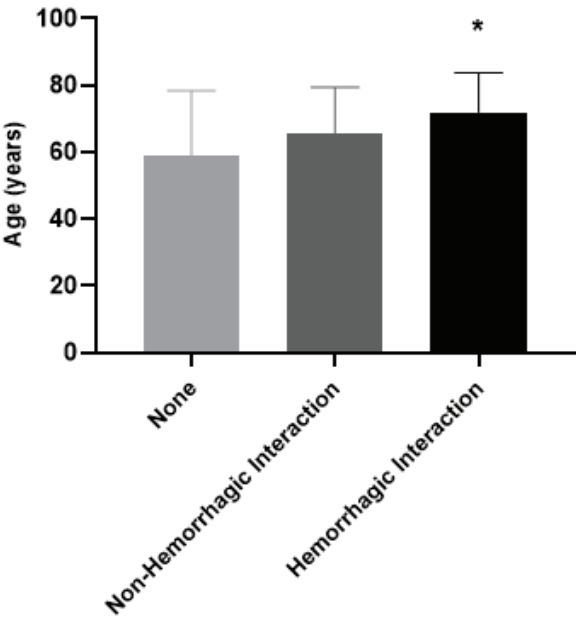


Figure 2. Age distribution across drug interaction groups

Table 3. Patient characteristics and clinical outcomes according to drug interaction status

Interaction Status	Number of Patients	Mean Age	Mortality (%)	Length of Hospital Stay (Mean)	Most Common Site of Hemorrhage
None	143	59.13 ± 19.29	42 ex	15 days	Intraparenchymal hemorrhage (45 patients)
Non-risk Interaction for Hemorrhagic Stroke	23	65.56 ± 13.87	9 ex	14.3 days	Brainstem hemorrhage (15 patients)
Hemorrhagic Stroke Risk Interaction	32	71.93 ± 11.73	12 ex	19.8 days	Cerebellar hemorrhage (19 patients)

stroke ($p = 0.0009$). No significant differences were identified between the other groups (Figure 2). When the prognoses were compared, although the rate of exitus was relatively higher in the group with drug interactions associated with hemorrhagic stroke risk, no statistically significant difference was observed between the groups in terms of prognosis ($p = 0.5052$). Although no statistically significant difference was found in the average length of hospital stay among the three groups, the group with the highest length of stay was again the group with drug interactions associated with hemorrhagic stroke risk ($p = 0.4190$). The average number of chronic diseases per patient was calculated as 0.81 in the non-interaction group, 2.0 in the group with interactions associated with hemorrhagic stroke risk, and 1.69 in the group with non-risk interactions. The presence of two or more chronic diseases showed a statistically significant difference according to drug interaction groups ($p < 0.0001$). This rate was lower in the non-interaction group and higher in the groups with interactions. When the distribution of hypertension, the most frequently observed comorbidity, was examined across the drug interaction groups, 39 patients (male = 25, female = 14) in the non-interaction group, 16 patients (male = 10, female = 6) in the non-risk interaction group, and 27 patients (male = 17, female = 10) in the hemorrhagic stroke risk interaction group were found to have hypertension. The frequency of hypertension differed significantly across interaction groups (Chi-square test, $p < 0.0001$). In particular, the prevalence of hypertension was markedly higher in the drug interaction group associated with hemorrhagic stroke risk. Although hypertension was more frequently observed in male patients within the hemorrhagic stroke risk interaction group, this difference was not statistically significant ($p = 0.9213$). When the interactions in the hemorrhagic stroke risk group were examined, a total of 30 interactions potentially causing high blood pressure were identified in 21 patients; 12 bleeding-related interactions in 10 patients; and 2 interactions potentially leading to irregular heart rhythm in 2 patients.

Discussion

Among the 198 patients included in the study, an analysis of demographic data revealed that 68% ($n = 135$) were male and 32% ($n = 63$) were female. A 2020 study investigating potential drug-drug interactions (DDIs) in 177 patients diagnosed with either hemorrhagic or ischemic stroke reported a similar gender distribution, with 64% male and 36% female patients [18]. Likewise, another study published in the same year involving 3,233 patients showed a comparable distribution [19]. The higher prevalence of hemorrhagic stroke in males may be related to the greater incidence of hypertension in men [20,21]; similarly, in our study, hypertension was more frequently observed among male patients in the group with

DDIs associated with hemorrhagic stroke risk. According to our findings, the mean age of the patients was 61.93 (± 18.2) years. In a study by Neves et al. involving over 500,000 stroke patients, the average age was similarly reported as 63.5 (± 16.6) years [22]. The mean age of male patients was 59.38 (± 17.9), while that of female patients was 67.5 (± 17.9). The lower number of female patients and their higher average age may be attributed to the neuroprotective effects of estrogen, which supports cerebral capillary health and reduces stroke risk in women [23]. Existing literature indicates that comorbidities are common in stroke patients, particularly those with hemorrhagic stroke. Consistent with our findings, the most frequent comorbidities reported are hypertension, diabetes mellitus, and dyslipidemia [22]. Although hemorrhagic stroke is less common compared to other types of stroke, it is known to have higher mortality rates. Mortality can vary between 25% and 60%, depending on various factors such as age, sex, presence of comorbidities, and the localization of the hemorrhage [24]. In our study, 31.3% of the patients were found to have died. Although limited in number, studies evaluating potential DDIs in patients with hemorrhagic stroke have suggested that 56.1% of the patients in our sample had used at least one medication within the last six months, and nearly half of them had potential drug-drug interactions. This highlights the importance of thorough medication history-taking. When patients were grouped based on the presence of potential interactions, it was notable that the mean age in the group with DDIs associated with hemorrhagic stroke risk was significantly higher than in the non-interaction group. This finding may be explained by the greater prevalence of polypharmacy in elderly individuals. It also suggests that advanced age may increase susceptibility to drug interactions that elevate bleeding risk due to pharmacokinetic and pharmacodynamic changes [25]. Although not statistically significant, the higher mortality rate and longer hospital stays in the group with hemorrhagic-risk DDIs are important clinical findings. These results suggest that certain drug interactions may complicate the clinical picture, worsen prognosis, and could potentially reach statistical significance with a larger sample size. The significantly higher prevalence of chronic diseases in the interaction groups underscores that polypharmacy and drug-drug interactions are markedly more frequent among individuals with multiple comorbidities. Consistent with the literature, hypertension was the most frequently observed comorbidity among patients with hemorrhagic stroke, particularly in those with drug interactions associated with hemorrhagic risk. It is known that certain drug combinations can elevate blood pressure or reduce the

effectiveness of antihypertensive therapies. Notably, our findings showed that a significant portion of drug interactions associated with hemorrhagic risk had the potential to induce hypertension. Given that hypertension is a major risk factor for hemorrhagic stroke, this finding holds considerable clinical importance.

Limitation

Our study has several limitations due to its retrospective design. Information regarding patients' medication use includes only drugs prescribed within the hospital system where the study was conducted. Medications obtained from other hospitals, healthcare institutions, or over-the-counter drugs without a prescription were not captured in our data. Despite these limitations, since the data were obtained from the largest and sole central hospital in the city, the results may be representative and provide valuable insights for future studies.

Conclusion

In conclusion, although hemorrhagic stroke remains a significant cause of morbidity and mortality worldwide, drug-drug interactions and their associated clinical consequences represent a modifiable risk factor in the management of these patients. Therefore, a detailed medication history should be carefully reviewed in patients with hemorrhagic stroke, and potential drug-drug interactions must be thoroughly assessed. Particular attention should be paid to elderly and multimorbid patients, and polypharmacy should be avoided whenever possible—especially in individuals receiving antihypertensive treatment, where the risk of clinically significant interactions may be higher.

Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and Human Rights Statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

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Conflict of Interest

The authors declare that there is no conflict of interest.

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